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INTRATHYROIDAL IODIDE BINDING RATES AND PLASMA METHIMAZOLE CONCENTRATIONS IN HYPERTHYROID PATIENTS ON SMALL DOSES OF CARBIMAZOLE

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1 The effect of small doses of carbimazole on the binding rate constant of intrathyroidal iodide, plasma methimazole concentrations and circulating thyroid hormone concentrations in five hyperthyroid patients is presented.

2 In all patients there was a marked reduction in iodide binding with carbimazole doses as low as 5 to 10 mg daily.

3 In three patients little further reduction in the observed binding rate occurred with daily doses in excess of 10 mg despite progressive increases in plasma methimazole concentrations.

4 At the end of 4 weeks' treatment with 10 mg carbimazole daily, the reduction in thyroid hormone concentrations and clinical improvement were such as to suggest that this dose may be an effective starting dose in many patients.

Introduction

Carbimazole is the most widely used antithyroid drug in Britain for the treatment of hyperthyroid patients. The recommended starting dose is 30 to 60 mg daily in three to four divided doses, which can be reduced to a lower maintenance dose of 5 to 20 mg daily without loss of control (Solomon, 1978) when the patient becomes euthyroid. In this paper the plasma methimazole concentrations, the intrathyroidal iodide binding rate constant and the concentration of circulating thyroid hormones are examined in a small group of hyperthyroid patients receiving low doses of carbimazole. The study is the preliminary part of a larger one designed to test the hypothesis that the normally recommended starting doses of antithyroid drugs are unnecessarily high in many cases.

Methods

Patients

Five previously untreated hyperthyroid patients with diffuse toxic goitre confirmed by radionuclide imaging were studied. The patients' clinical details are set out in Table 1. Carbimazole was given orally at twelve-hourly intervals. As a preliminary study the first patient (A) agreed to be hospitalised and was treated with 5 mg/day for the first week. The dose was increased at weekly intervals to 10, 20, 30 and 40 mg/day during subsequent weeks. The four other patients (B, C. D, and E), who were out-patients, received 10 mg of carbimazole daily for the first 4 weeks. The dose was increased to 20 mg and then 30 mg per day during the subsequent four-weekly periods (patient D received 10 mg of carbimazole daily for 3 weeks only).

Table 1 Clinical details of patients

Patient	*Age (years)*	*Sex*	*Weight (kg)*	*Duration of symptoms before therapy (months)*
A	53	F	58	4
B	28	F	41	24
C	30	F	45	6
D	47	F	52	5
E	26	F	51	18

Venous blood was sampled from patient A 6 h after

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the dose on 3 to 4 days of each weekly treatment period. In the remaining four patients, blood was sampled weekly 5 h after a dose of carbimazole. The thyroid hormone concentrations in these samples were measured by radioimmunoassay and the plasma methimazole and 3-methyl-2-thiohydantoin concentrations by high-performance liquid chromatography (Skellern *et al.*, 1980).

Kinetic analysis

The kinetics of thyroidal uptake of intravenous ^{132}I-iodide (50 μCi) in these patients were investigated before treatment and on the last day of each treatment period. This consisted of serial measurements of thyroidal uptake, using an uptake counter (Hilditch & Alexander, 1980), followed by a perchlorate discharge test (300 mg of sodium perchlorate given intravenously) after 1 h. Several blood samples were taken during the test for measurement of plasma radioactivity. Each kinetic study was performed six hours after the dose in patient A and approximately 5 h after the dose in the other four patients. The uptake data was analysed on the basis of an open three-compartment binding model of the gland using an improved least sum of squares method (Hilditch & Alexander, 1980). This analysis gave an estimate of the binding rate constant of intrathyroidal iodide which was verified by the result of the perchlorate discharge test (Hilditch, Horton & Alexander, 1980).

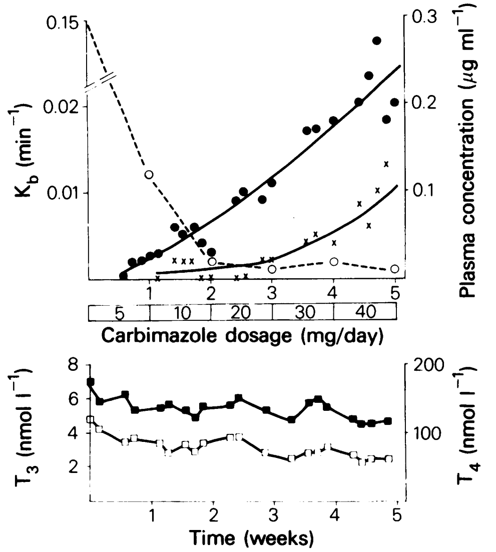

Figure 1 Variation of the iodide binding rate constant (K_b, O) and plasma methimazole (●), 3-methyl-2-thiohydantoin (3-MTH, ×) and thyroid hormone concentrations (T_3 □, T_4 ■) with increasing weekly doses of carbimazole in patient A.

Results

The results from patient A in whom the dose of carbimazole was increased weekly are shown in Figure 1 where a reduction in the iodide binding rate constant (K_b) is observed as the plasma methimazole and 3-methyl-2-thiohydantoin concentrations increase steadily, reaching values of 0.27 μg ml^{-1} and 0.14 μg ml^{-1} respectively. A marked reduction in the iodide binding rate constant was observed at the lowest daily dose of 5mg/day. Binding inhibition was greater at 10 mg/day but there was little further effect for doses greater than 10 mg/day.

The effect of increasing the dose of carbimazole on a four-weekly basis on the iodide binding rate constant, plasma hormone concentrations and clinical status, as reflected by a therapeutic index (Crooks, Wayne & Robb, 1960), in patients B, C, D and E is shown in Table 2, with the mean value of the plasma concentrations of methimazole observed during each four-weekly treatment period. Patients B and C were similar to patient A in that there was little to be gained in terms of reducing binding by increasing the dose beyond 10 mg/day. All patients improved clinically and patient C became biochemically euthyroid after 4 weeks' treatment with 10 mg/day carbimazole. The monthly mean values of the binding rate constant (K_b) and the weekly mean plasma methimazole and thyroid hormone concentrations for these patients are shown in Figure 2. There was a marked effect overall on the iodide binding rate constant with a daily carbimazole dose of 10 mg.

Figure 3 shows the relationship between the binding rate constant and the plasma methimazole concentrations at the time of the iodide kinetic study in patients B, C, D and E. Intrathyroidal iodide binding would appear to be markedly inhibited at plasma methimazole concentrations greater than 0.1 μg ml^{-1}.

Discussion

Carbimazole, the 3-carbethoxy derivative of methimazole, is rapidly metabolised in man to methimazole, which is then further metabolised to 3-methyl-2-thiohydantoin (Skellern *et al.*, 1980). Methimazole has been shown to reduce the production of thyroid hormones by inhibiting the iodination of thyroglobulin and the coupling of iodinated tyrosyl residues (Gilman & Murad, 1975). There is evidence to suggest that 3-methyl-2-thiohydantoin, of which the plasma concentrations were determined in patient A (Figure 1) may act similarly (Skellern, Mahmoudian & Knight, 1979).

The present study was an attempt to measure intrathyroidal iodide binding directly and to observe how it varied with plasma methimazole concentrations in patients receiving incremental doses of carbimazole.

Table 2 Effect of different doses of carbimazole on intrathyroidal iodide binding, thyroid hormone concentrations and clinical status in 4 hyperthyroid patients (each treatment period with a given dose lasted 4 weeks)

Carbimazole dose (mg/day)	*Patient*	*Plasma concentration at time of iodide kinetic study (nmol l^{-1})*		*Therapeutic index at time of iodide kinetic study**	*Binding rate constant (min^{-1})*	*Mean plasma methimazole concentration during treatment period ($\mu g\ ml^{-1}$)*
		T_3^+	T_4^{++}			
Before treatment	B	5.8	196	18	>0.150	—
	C	7.1	200	31	>0.150	—
	D	10.1	238	27	>0.150	—
	E	5.8	184	24	>0.150	—
10	B	3.8	127	13	0.005	0.05
	C	2.5	103	11	0.006	0.03
	D	3.8	118	11	0.050	0.02
	E	2.9	121	7	0.023	0.03
20	B	2.3	74	5	0.003	0.12
	C	1.3	34	4	0.004	0.08
	D	1.4	22	2	0.009	0.03
	E	1.3	45	0	0.012	0.07
30	B	1.5	34	6	0.002	0.34
	C	1.5	32	7	0.001	0.19
	D	0.6	22	1	0.006	0.07
	E	1.0	30	2	>0.150**	0.14

$^+$ Normal T_3 range 0.9 to 2.8 nmol l^{-1}
$^{++}$ Normal T_4 range 55 to 144 nmol l^{-1}
* 0–5 indicates fully controlled hyperthyroidism
** no methimazole detected in plasma at time of kinetic study due to patient's non-compliance; this zero methimazole value is not included in the mean value of the last column.

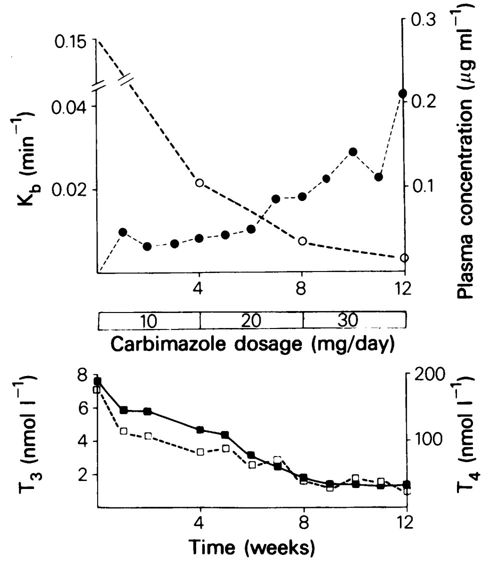

Figure 2 Variation of the mean iodide binding rate constant (K_b, ○) and mean plasma methimazole (●) and thyroid hormone concentrations (T_3 □, T_4 ■) with increasing doses of carbimazole, in patients B to E.

Concurrent changes in the concentration of circulating thyroid hormone and clinical response of the patients were also investigated.

Although the binding rate constant was measured at 5 to 6 h after the oral dose of carbimazole, and its value may differ from the binding rate constant at other times, the results should reflect the relative effectiveness of the daily dose studied because the analyses were performed at the same time after the drug was given. Similarly the measured methimazole plasma concentrations do not necessarily represent the mean plasma concentration for a particular daily dose of carbimazole, but they should reflect a given dose since they were taken at the same time (5 or 6 h) after the carbimazole dose.

The results show that carbimazole in doses as little as 5 to 10 mg/day has a marked effect on iodide binding, reducing the observed binding rate constant from > 0.15 min^{-1} to 0.05 min^{-1} or less (Figures 1 and 2). A daily dose of 10 mg was sufficient to reduce the circulating thyroid hormone concentrations in patients B to E, with one patient (C) becoming biochemically euthyroid after 4 weeks' treatment (Table 1). All four patients became clinically and biochemically euthyroid whilst receiving 20 mg/day. Because there is a delay of 4 to 8 weeks between the start of antithyroid drug administration and reversion of circulating thyroid

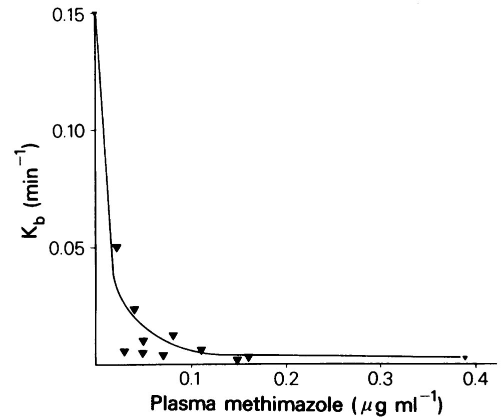

Figure 3 Iodide binding rate constants (K_b) in patients B to E plotted against the plasma methimazole concentration at the time the binding rate constant was determined.

hormones to euthyroid levels (DeGroot & Stanbury, 1975), the dose increment may not have been necessary to reduce hormone levels to the euthyroid range. It may well be that all four patients would have become euthyroid on 10 mg carbimazole a day. Moreover the inhibition of the production of the thyroid hormones may be partly attributable to 3-methyl-2-thiohydantoin which has a plasma half-life at least three times longer than methimazole (Skellern *et al.*, 1980), and has been detected in thyroid tissues of patients receiving either carbimazole or methimazole (Skellern *et al.*, 1977).

The present findings contrast with previous results which suggested that 10 mg methimazole daily would not achieve sufficient inhibition of iodide binding (Berson & Yallow, 1955). A longer study on a larger group of patients would seem to be justified to prove whether treatment of hyperthyroidism with carbimazole, 10 mg daily, is effective in achieving the euthyroid state.

Treatment at this low dose might reduce the incidence of methimazole toxicity (Wiberg & Nuttal, 1972; Fischer, Nayer & Miller, 1973; McGavack & Chevalley, 1954) and would be desirable in the treatment of hyperthyroidism in pregnancy to ensure that foetal hypothyroidism is avoided (Hamburger, 1972).

There would appear to be a relationship between the intrathyroidal iodide binding rate constant and the plasma methimazole concentration at the time of the iodide kinetic investigation (Figure 3). The reduction in the binding rate constant is so great that its value has been reduced by a factor greater than 3, before plasma methimazole can be quantitatively measured (0.02 μg ml^{-1}). At methimazole concentrations greater than 0.1 μg ml^{-1} the iodide binding rate constant has reached negligible proportions.

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